CHARGE NUMBER: 2500

PROJECT TITLE: Synthesis of Tobacco Additives

PROJECT LEADER: J. I. Seeman

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## I. Nicotine Chemistry

For the first time, the individual enantiomers of 6-methylnicotine have been successfully prepared and purified.[1] Free radical methylation of (-)-nicotine with t-butylhydroperoxide and ferrous sulfate afforded (-)-6-methylnicotine. The same reaction with (+)-nicotine yielded (+)-6-methylnicotine. These compounds appear to be nearly optically pure. The specific rotation of (+)-6-methylnicotine was found to be $+175^{o}$. These enantiomers are of great importance for our pharmacological and behavioral studies due to the fact that racemic 6-methylnicotine is known to possess pharmacological activity on a par with nicotine.

The major study concerning the methylation of nicotine is nearing completion. The product mixtures from eight of the methylation runs were subjected to HPLC purification. The components of each mixture were successfully separated and isolated, and optical rotations were obtained.[2] Methyllithium additions to nicotine result in partially racemized products with 6-methylnicotine undergoing the greatest racemization in most cases. On the other hand, radical methylation of nicotine provides products with high optical rotations. The radical methylation approach appears to be the method of choice for obtaining analogs in high enantiomeric excess.

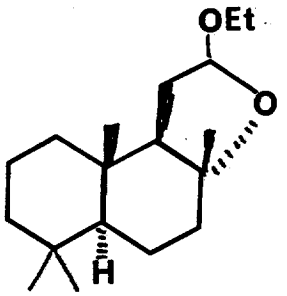
A number of nicotinoids were prepared and purified for a variety of studies. Additional 6-(2-hydroxyethyl)nicotine was synthesized for the ongoing collaborative study into the use of affinity chromatography for nicotine receptor isolation.[1,3] To assist us in an understanding of the mechanism of racemization during the addition of organolithium reagents to nicotine, 2'-deuteronicotine has been prepared.[1] A synthesis of 2'-methylnicotine free of the major byproduct, 6-methyl-2'-methylnicotine, was achieved.[1] The cis-and trans-5'-methylnornicotines were successfully separated and isolated by the use of HPLC.[2]

## II. Flavor Chemistry

For odor evaluation by multidimensional scaling a total of fifteen 2-monoalkyl and 2,3-dialkyl pyridines and pyrazines were prepared.[4]

Preparation of various 2,6-dialkylpyridines is also underway.[5] By the use of alkyllithium reagents, 2-t-butyl-6-ethylpyridine and 2-t-butyl-6-isopropylpyridine were synthesized. Attempts are continuing in an effort to prepare 2-ethyl-6-methylpyridine and 2-isopropyl-6-methylpyridine.[5]

The woody odorant isolated from the photo-oxygenation of abienol has been tentatively identified as structure I through the use of NMR spectrometry carried out by R. Cox.[4] Synthesis of the odorant is currently in progress. Reduction of sclariolide with DIBAL provided the lactol precursor to I as an epimeric mixture in quantitative yield.[4]

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III. Collaborative Studies

In conjunction with R. Izac, of Project 2525, the monomenthyl ester of a mixture of meso and d,l-2,3-dimethylsuccinic acids was prepared.[5] Separation of the isomers by HPLC is under study.[6] Derivatives of the acid have also been prepared.[5]

References;

1. H. Secor, 7566
2. D. Howe, 7575
3. C. Chaydarian, 7594
4. R. Southwick, 7446
5. L. Clawson, 7659
6. R. Izac, Project 2525

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